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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,259	01/26/2004	Xiao-Chun (Chris) Le	033110-004	6473

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EXAMINER	
WESSENDORF, TERESA D	

ART UNIT	PAPER NUMBER
1639	

NOTIFICATION DATE	DELIVERY MODE
12/12/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/763,259	LE, XIAO-CHUN (CHRIS)	
	Examiner	Art Unit	
	T. D. Wessendorf	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-4,11,12,16 and 24* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-4,11,12,16 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/9/07 has been entered.

Status of Claims

Claims 2-4, 11-12, 16 and 24 are pending and under examination.

Withdrawn Rejections

In view of the amendments to the claims and applicant's arguments the 35 USC 112, first and second paragraph rejections are withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 24 as amended, is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Non-sequitur in claim 24 of "**the** laser-induced fluorescence polarization".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 2, 11-12, 16 and 24, as amended, are rejected under 35 U.S.C. 102(a) as being anticipated by Wan et al(Analytical Chemistry (2000)).

Wan discloses throughout the article, e.g., at page 5583, Abstract:

> Protein-DNA interactions were studied on the basis of **capillary electrophoretic separation of bound from free fluorescent probe followed by online detection with laser-induced fluorescence polarization. Changes in electrophoretic mobility and fluorescence anisotropy upon complex formation were monitored for the determination of binding affinity and stoichiometry.** The method was applied to study the interactions of single-stranded DNA binding protein (SSB) with synthetic oligonucleotides and single-

stranded DNA. Increases in fluorescence anisotropy and decreases in electrophoretic mobility upon their binding to SSB were observed for the fluorescently labeled 11-mer and 37-mer oligonucleotide probes. Fluorescence anisotropy and electrophoretic mobility were used to determine the binding consts. of the SSB with the 11-mer(5+106 M-1) and the 37-mer (23+106 M-1). Alternatively, a fluorescently labeled SSB was used as a probe, and the formation of multiple protein-DNA complexes that differ in stoichiometry was observed. The results demonstrate the applicability of the method to study complex interactions between protein and DNA.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 103

Claims 2-4, 11-12, 16 and 24, as amended, are rejected under 35 U.S.C. 103(a) as being unpatentable over Laing (6,331,392) in view of Le et al (6,132,968).

Laing discloses (throughout the Patent disclosure) at e.g., the abstract, a method for screening for bioactive compounds in particular those that bind to RNA sequences by assessing the stability and/or the conformation of an RNA target in the presence and absence of test ligands (complex formation, as claimed), and identifying as a ligand any test ligand that causes a measurable change in target RNA stability and/or conformation. The effect of a ligand on target RNA stability and/or conformation is assessed by measuring the fluorescence polarization of a fluorescently labeled probe. Probes include

molecules, which comprise fluorescent moieties whose measurable fluorescence properties, particularly polarization are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Probe is any molecule to which a fluorescent moiety is attached, in which one or more fluorescence properties are sensitive to the stability and/or conformation of the target RNA and/or to the binding state of the probe. Suitable probe compounds include without limitation nucleic acids, particularly oligonucleotides; small RNA-binding molecules exemplified by 2-deoxystreptamine antibiotics, which bind the Rev-responsive element in HIV RNA, or other compounds that specifically recognize the major or minor groove of RNA; and proteins, and peptides derived therefrom, that recognize particular RNA sequences or conformations. See also Fig. 1. Test ligands may be derived from large libraries of synthetic or natural compounds. For example, synthetic compound libraries are commercially available. See the specifics of the method in Example 1.

Laing further discloses at e.g., col.3, lines 15-21:

> Probes useful in practicing the invention include molecules which comprise fluorescent moieties whose measurable fluoresence properties, particularly polarization or anisotropy, are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe.

Laing further discloses the stoichiometry i.e., ratios at e.g., col.8, line 1 up to col. 9, line 20:

> …determination of the absolute amounts or ratios of stabilized and non-stabilized or folded and unfolded target RNA may be carried out using probes which comprise one or more fluorescent moieties. Any stability-sensitive and/or conformation-sensitive probe to which an appropriate fluorescence moiety can be attached may be used in practicing the invention. For example, an oligonucleotide can be designed so that it will hybridize to a particular RNA target only when the RNA is in an unfolded conformation or to single-stranded regions in an otherwise folded conformation.

Laing does not disclose the use of capillary electrophoresis as recited in claim 2. However, Le discloses, throughout the Patent disclosure, electrokinetic chromatography by incorporating the teachings of Hjerten at e.g., col. 18, lines 45-57:

> The specificity of the methods provided herein is further enhanced by the use of capillary electrophoresis to separate fluorescent and non-fluorescent molecular entities. Capillary electrophoresis is described by Hjerten et al., U.S. Pat. No. 5,114,551, the entire contents of which are hereby incorporated by reference. Capillary electrophoresis includes the use of capillaries which are filled either with a gel (e.g., polyacrylamide) or with buffer. The use of capillary electrophoresis in the methods of the invention provides rapid sample analysis and permits the use of small sample volumes, making it particularly useful for analyzing samples of biological interest [See, e.g., Xian et al. (1996) Proc. Natl. Acad. Sci. USA 93:86-90].

Le further discloses at e.g., col.8, lines 30-50:

> Importantly, the methods of the invention are more accurate than prior art methods since they avoid potential artifacts which are caused by chemical or enzymatic nucleic digestion. Instead, the methods of the invention limit

> sample manipulation to extraction of nucleic acid sequences, incubation of the extracted nucleic acid sequences with proteins which are specific for the nucleic acid modification of interest and with nucleic acid sequence modification-specific molecules, and capillary electrophoresis.

Accordingly, it would have been obvious to one having ordinary skill in the art at the time the invention was made to use electrokinetic chromatography(EC) as capillary electrophoresis (CE) separation in the method of Laing as taught by Le above. Le teaches that said EC, particularly, CE is an accurate method that avoid potential artifacts caused by chemical or enzymatic nucleic digestion. One having ordinary skill in the art would have been motivated to use a capillary electrophoresis in the method of Laing for the advantages derived in said use as taught by Le above. One would reasonably expect that the use of said chromatography in the method of Laing would result in the separation of the bound from unbound complex since the technique of chromatography has been known and employed in the art for such separation. Furthermore, it would have been obvious to determine the result effective variables such as the stoichemistry of a complex(compound) and /or binding affinity and correlate the results of one technique to the other. Such correlation would expectedly provide accurate quantitative or qualitative measurement of the complex being determined.

Response to Arguments

Applicant states that the method of Laing is directed to identifying conformational changes in RNA. The method allegedly detects the conformational change in a target RNA sequence when the hybridization of a fluorescently labeled probe is inhibited or modified through the interactions of a ligand with the target RNA sequence. The method of Le is directed to detecting and/or quantitating at least one modification to a nucleic acid sequence of interest. Le cites the use of fluorescently labeled polypeptides as one exemplary method of identifying a modification to a nucleic acid sequence. Neither Laing or Le suggest a method of determining the binding affinity and/or stoichiometry between a binding factor and a probe by combining information obtained from electrokinetic chromatography and laser-induced fluorescence polarization. The subject matter of amended claim 24 encompasses correlating the information obtained from these two techniques so that the binding affinity and/or stoichiometry between a probe and a binding factor can be determined. Neither Laing nor Le, separately or in combination, teaches the method set forth in amended claim 24.

In reply, attention is directed to the cited section of Laing's disclosure at e.g., col. 8 for teaching the stoichiometry measurement (i.e., ratios) and binding at e.g., col. 3. It would

be within the ordinary skill in the art to correlate the results between two techniques of analysis for accurate determination or analysis of the complex being determined or studied.

> Where the combination of old elements performed a useful function, but it added nothing to the nature and quality of the subject matter already patented, the patent failed under §103. KSR v. Teleflex, 17 S. Ct. 1727, 82 USPQ 2d 1385 (2007).

Double Patenting

Claims 2, 11, 16 and 24, as amended, are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 and 9 of U.S. Patent No. 6,132,968('968 Patent) in view of 6,331,392 ('392 Patent) for reasons reiterated below.

The claims and specification of the '968 Patent claims/discloses a method for quantitating at least one modification of interest in a nucleic acid sequence contained in a sample, comprising: a) providing: i) a sample suspected of containing a nucleic acid sequence comprising the at least one modification of interest; ii) a first polypeptide sequence capable of specifically binding to the at least one modification of interest, and iii) a fluorescently labeled second polypeptide sequence capable of specifically binding to the first polypeptide sequence; b) combining the sample, the first polypeptide sequence and the fluorescently labeled second polypeptide sequence to produce a fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, (step b, as claimed) and a fluorescently labeled second polypeptide sequence:first polypeptide sequence complex; c) separating the fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, the fluorescently labeled second polypeptide sequence:first polypeptide sequence complex and the fluorescently labeled second polypeptide sequence by capillary

electrophoresis; d) detecting the separated fluorescently labeled second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex by laser-induced fluorescence; and e) quantitating the separated second polypeptide sequence:first polypeptide sequence:nucleic acid sequence complex, thereby quantitating the at least one modification of interest in the nucleic acid sequence. Example 1, col. 20 up to Example 6, col. 27 provides detail steps of the method and the specific probes and polypeptides used in the method. The '968 Patent does not disclose fluorescence polarization. However, the '392 patent discloses the alternativeness of fluorescence and fluorescence polarization. It further discloses that particularly polarization are sensitive to the stability and/or conformation of the target RNA as reflected in the binding state of the probe. Accordingly, one would have been motivated to use fluorescence polarization in the method of the '968 Patent for the benefits derived therein as taught by the '392 Patent.

Response to Arguments

Applicant states that this provisional rejection is moot with regard to canceled claim 1. In addition, this provisional rejection is moot with regard to claims 2, 11, and 16, as they now depend from claim 24. Accordingly, Applicants contend that the instant claims are patentably distinguishable over the '968 patent, in view of the '392 patent, and respectfully request withdrawal of the provisional obviousness-type double patenting rejection.

In reply, this is an obviousness double patenting rejection not a provisional obviousness patenting rejection as the rejection is based on an issued patent. Even with the cancellation of claim 1 and amendments to claim 24, for example,

the rejection has not been overcome. The combined teachings of the references disclose all the elements of the claimed method that renders the claim prima facie obvious.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to T. D. Wessendorf whose telephone number is(571) 272-0812. The examiner can normally be reached on Flexitime.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached on (571) 272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

T. D. Wessendorf
Primary Examiner
Art Unit 1639

tdw
November 19, 2007